Remarks

Claims 1, 3 - 13, and 15 - 17 are pending. The amendment to claim 1 is editorial.

Applicants gratefully acknowledge the withdrawal of the rejection of claims 1 and 3 -7 under 35 USC 102(b) as being anticipated by Shaw et al.

Claims 1, 3-7 and 10-13 were rejected under 35 USC 103(a) as being unpatentable over Shaw et al. According to the examiner's original statement of the rejection, Shaw teaches a screening method comprising providing a prodrug of PMPA, selecting plasma as a target tissue and intestine and liver as non-target tissue, administering prodrug to both tissues and determining the relative *in vitro* biological stability and bioavailability of the PMPA in the tissues. The examiner now concedes that plasma is not a target tissue, but instead advances the proposition that esterolytic degradation would have been "the same" as in whole blood. Therefore, according to the examiner, it would have been obvious to the artisan to use blood in place of plasma in the Shaw et al. method.

Shaw et al. are concerned with determining oral bioavailability of test compound. They were not concerned with relative tissue DISTRIBUTION of the cleavage product. They were simply investigating the hydrolytic stability of the prodrugs in tissues involved in oral administration of the prodrugs (intestines, plasma, liver). Shaw et al. did not have as their objective the determination of differential antiviral or antitumor activity in the tissues being sampled; they were simply looking at the stability of the prodrugs to hydrolysis (or their ability to pass through the gut into the circulation).

As applied to claim 1, Shaw et al. fails to meet the target tissue limitation. Plasma is not a tissue, which the examiner recognizes. Instead the examiner takes the position that it would have been obvious to use blood instead of plasma, arguing that blood contains esterolytic enzymes just like plasma. This is a whole cloth argument not based on any cited reference. If the examiner wishes to take the view that blood would be equivalent to plasma in the Shaw et al. then the examiner is

invited to provide a reference that supports this point of view. As it is, the record is devoid of such a citation. In any case, the proposition is clearly groundless. Blood contains cells. Blood cells such as moncytes, red blood cells and the like contain a unique complement of esterolytic enzymes. Phagocytes alone contain a diverse collection of enzymes designed to digest waste matter and invading organisms, none of which enzymes by definition is found in plasma. Blood certainly would not be esterolytically "equivalent" to plasma by any stretch of the imagination. If the examiner is interested, applicants would be happy to supply a citation pointing out that blood and plasma do not produce an equivalent hydrolytic profile against a given target ester.

Regardless, the claims also distinguish Shaw et al. in that they exclude intestine as a target tissue. Shaw et al. are devoid of any teaching or suggestion to omit intestinal homogenate from their study. On the contrary, intestine is critical to their work because it is a critical player in oral absorption/hydrolysis of prodrugs. It would have been inconceivable for Shaw et al. to omit the study of intestinal homogenate. Applicants' specification observes that intestine is not a preferred target tissue (specification page 11, lines 14 - 16), in keeping with the intent to exclude conventional bioavailability studies from the scope of the claims.

Claim 10 is particularly patentable over Shaw et al. The Shaw et al. administration of the prodrugs to live dogs also does not render claim 10 obvious. Shaw et al. were simply determining the ability of the prodrug to produce active drug in the circulation after oral administration. Shaw et al. do not disclose administering the prodrug and then assaying its conversion to parental drug <u>in target vis a vis non-target tissues</u>. Applicants' method contemplates determining *differential* activity in various tissues.

Fundamentally, nothing but hindsight motivates the rejection of claim 10. It is far less trouble to measure prodrug stability in tissue homogenates than in an intact animal, and the examiner has not provided any credible evidence for the assertion that "other variables" would direct the change. The enzymes, hormones and the like would be in the homogenates just as they are in whole animals. Shaw et al. use intact animals, but only for the conventional oral bioavailability study. The fact that they did not use intact animals instead of homogenates when looking at individual tissues is instructive that the use of intact animals would not have been obvious for the

individual tissues. Further, in any case, it would not have been obvious to omit the intestinal assay from Shaw et al. because this was critical in determining oral bioavailability.

The Office is respectfully requested to reconsider and withdraw the rejection under 35 USC 103 over Shaw et al.

Claims 1, 3-7, 9-13, 15 and 16 were rejected under 35 USC 103(a) as unpatentable over Shaw et al. in view of Glazier et al. The examiner takes the view that it would have been obvious to "combine" the screening methods of these references because both are "the determination of the relative antiviral activities of phosphonoamidate prodrugs in various tissue types". This rejection is respectfully traversed.

Glazier et al. was deficient because it does not teach determining antiviral activity in *different* tissues. Instead, Glazier et al. was comparing activity of the test compounds in paired infected and uninfected cells (from the same tissues).

Shaw et al., on the other hand, have an entirely different objective. They are not looking at antiviral activity, they are looking at prodrug stability in individual tissues. Their objective is to measure the convertibility of the prodrug to parental drug in intestinal and liver homogenates. They are not concerned with whether the parental drug has any antiviral activity IN the various tissues – they already knew that.

There is no basis for combining these references except hindsight, and even then the combination would not reach the claims. Combining Glazier et al. with Shaw et al. would have Shaw et al. testing stability in infected homogenates and uninfected homogenates. In addition, there would be no reason to drop the intestinal homogenate since it is central to the Shaw et al. inquiry.

The examiner is respectfully requested to reconsider and withdraw this rejection.

Claims 1, 3 - 8, 10 - 13 and 17 were rejected under 35 USC 103(a) as being unpatentable over Shaw et al. in view of Starrett et al. This rejection appears to apply to only to claim 8 (which

calls for an aryl ester prodrug) and claim 17 (where the tissue is hematological and the activity is antitumor activity). This rejection is respectfully traversed.

According to the examiner, Starrett et al. teaches administering a PMEA prodrug to rats and assaying the appearance of the parental drug in urine. PMEA is reported by Starrett et al. to have anti-tumor activity. Shaw is determining bioavailability and tissue stability of a prodrug. The examiner suggests that it would have been obvious to combine the two references because both are concerned with "bioavailability of prodrugs in animals." This rejection is respectfully traversed.

Starrett et al. does not teach or suggest omitting the intestinal homogenate of Shaw et al. Starrett et al. is simply duplicative to the bioavailability study of Shaw et al. The only difference is that Starrett et al. measured bioavailability by looking for the metabolite in the urine; Shaw et al. looked for it in the plasma. Starrett et al. therefore teach away from the examiner's proposition that it would have been obvious to study stability in blood rather than plasma. Starrett et al. would suggest, if anything, that one should look for metabolic products in the urine, not in blood. Starrett et al. does not remedy any of the deficiencies of Shaw et al. The examiner is respectfully requested to reconsider and withdraw this rejection.

This application is now believed to be in condition for allowance. An early notice to that effect is solicited.

Respectfully submitted,

Max Hensley, Reg. 27,043

GILEAD SCIENCES, INC.

333 Lakeside Drive

Foster City, CA 94404

Phone: (650) 522-1963

Fax: (650) 522-5575

Date: 4/4/18